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Disease-a-Month

Gout

JOHN H. TALBOTT

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Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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John H. Talbott

is a graduate of Harvard Medical School. Following an internship at the Presbyterian Hospital in the city of New York, he was a tutor in Biochemistry at Harvard College and a member of the faculty at Harvard Medical School. While in Boston he carried out his studies on metabolic diseases at the Harvard Fatigue Laboratory and the Massachusetts General Hospital. Since 1946 he has been Professor of Medicine at the University of Buffalo School of Medicine and Physician-in-Chief, Buffalo General Hospital. His research interests include gout and connective tissue disorders.

GOUT is an honorable malady, if such an adjective can be applied justifiably to a morbid process. It was recognized as a clinical entity before the birth of Christ and is one of the few diseases that has responded to a specific therapeutic agent for a number of centuries. Also, the number of eminent persons afflicted with gout that have come down to us through the pages of history is significant.

The discovery of a urate tophus in the great toe of a skeleton in a cemetery in upper Egypt is proof of the fact that the disease was present a thousand years or more before the birth of Christ. The use of hermodactyl by Alexander of Tralles in the sixth century A.D. is one of the earliest records of the employment of Colchicum in arthritic disorders (7). The malady was known as podagra prior to the twelfth century, at which time the term gout was introduced; thereafter the terms were used interchangeably. A partial list of sufferers includes Martin Luther, Henry VIII, Charles the Great, John Calvin, John Wesley, William Harvey, Francis Bacon, Milton, Cromwell, Alexander the Great, Lord Chesterfield, the William Pitts, Benjamin Franklin, Samuel Johnson, Sydenham, Newton, Goethe, Charles Darwin and Charles II. In the latter part of the eighteenth century, Wollaston isolated uric acid from gouty tophi and not many years later Forbes

postulated that gout was associated with an increased concentration of uric acid in body fluids. Evidence in support of this speculation was produced in 1848 by Garrod.

TERMINOLOGY

The terms currently in use in discussing the metabolic dyscrasia are gout, gouty arthritis, intercritical period and chronic tophaceous gout. *Gout* is the parent term without reference to articular symptoms. It is justified in the case of any person who has experienced one or more acute attacks of gouty arthritis. The only abnormality that may be demonstrated in such a person is an increase in the concentration of urate in serum and, in a percentage of individuals, an increased excretion of uric acid in the urine. *Acute gouty arthritis* is a descriptive term. It refers to the acute articular episode and usually is the reason for the patient's seeking medical advice. *The intercritical period* also is descriptive and, in the absence of chronic deforming changes, it is associated with no articular distress and imposes no limitation of motion on affected joints. The intercritical period, or, as we would like to label it now, *the prophylactic period*, should occupy but a small part of the time of any patient afflicted with the malady. The more effective the prophylactic regimen the longer should be the period between acute articular attacks. *Chronic tophaceous gout* is the fate of a small number of patients only. It is a late manifestation and several decades usually have elapsed following the first attack of acute gouty arthritis before this stage may be manifest (Plate 1, p. 17). If the treatment currently available is effective, the chronic tophaceous stage should become a decreasingly important clinical problem and be seen less and less frequently. There remains yet another term, *gouty diathesis*, that appears in some medical writings. This may refer to coronary vessel disease, generalized arteriosclerosis, gastrointestinal symptoms, skin eruptions or other clinical manifestations that are considered by us to be no more than casually related to gout. On the other hand, it is believed that the term gouty diathesis is applicable to those members of gouty families who have the metabolic fault without clinical manifestations of gouty arthritis. Lastly the terms *urate* and *uric acid* will be used interchangeably in this discussion. Urate refers to the anion salt of uric acid and is preferred as a chemical reference just

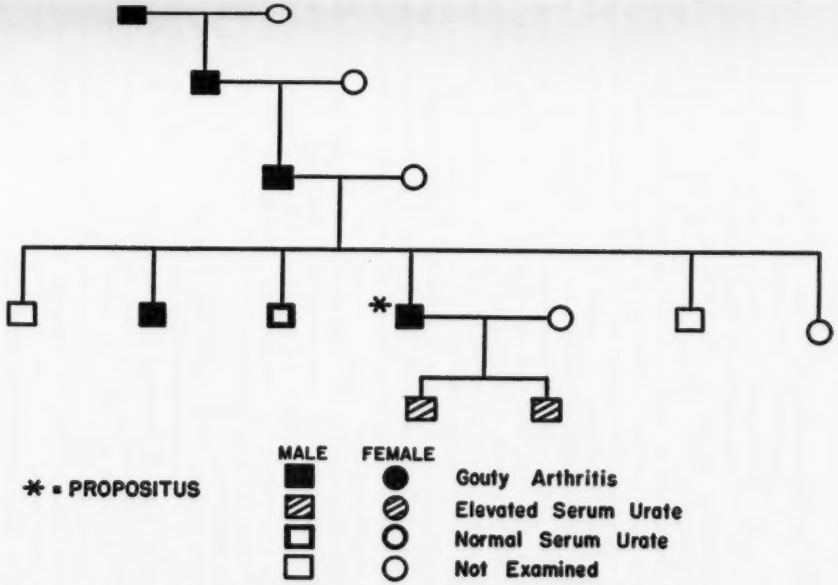

FIG. 1.—Genealogic observations on a family with gout.

as chloride is preferred to hydrochloric acid in considering this electrolyte in body economy.

HEREDITY

The hereditary nature of gout has been recognized since the time of Hippocrates. Returning to more recent times, Garrod and Scudamore reported a significant familial incidence. We believe that the failure to discover a higher family incidence in contemporary series is related to the lack of zeal with which this datum is sought. Figure 1 presents selective data from a family in which several generations have been afflicted with the clinical malady; other members have an increased concentration of uric acid in the serum without clinical or laboratory evidence of articular involvement. From a series of patients studied by us at the Buffalo General Hospital, the family incidence is more than 50%. Equally important is the fact that one in five of the relatives of gouty patients will have a concentration of uric acid in the serum that is in the gouty range. Smyth and associates (10) concluded from their observations that hyperuricemia was apparently due to a single autosomal dominant while Hague and Harvald (8) favored the theory of a monomeric dominant with a cumulative gene action, as is the case for normal characters in general.

The age at which the increase in concentration occurs in nonaffected relatives has not been determined. Selected data from our studies indicate that the transition from the normal to the hyperuricemic range occurs during adolescence. When confronted with an increase in the concentration of uric acid in the serum of nonaffected relatives, we have recommended a conservative course. The information is made known to the family but neither colchicine nor a uricosuric agent is recommended in treatment. We practice a policy of waiting until the first articular episode appears. At the present time there has been no cause to regret this policy. The incidence of individuals with hyperuricemia developing subsequently acute gouty arthritis has been low in our series. Undoubtedly, this experience biases us in favor of a conservative course prior to the first articular bout.

INCIDENCE

The incidence of gout is considerably higher than tentatively assumed by a number of physicians. Those particularly

interested in the malady, however, appreciate the relative frequence from their clinical experience. The incidence is not related to a particular social stratum or standard of living. If gout were considered more often in the differential diagnosis of unexplained acute articular distress, and the diagnostic criteria pursued, the incidence undoubtedly would rise. There is the tendency among some physicians to disregard the likelihood of gouty arthritis in the absence of advanced tophaceous changes. There is also a tendency to place undue reliance on the significance of the concentration of serum urate as determined in the routine biochemical laboratory. The determination of uric acid is tricky and the values frequently are misleading or equivocal. Gout is predominantly a disease of the male. The ratio is approximately 20:1 in favor of members of this sex. In our experience, the diagnosis is somewhat more difficult to clinch in a female and particular care should be exercised in pursuing the diagnostic criteria to the logical conclusion. There are several females with chronic tophaceous gout in our series in which the usual experience reveals a diagnostic problem with an equivocal clinical history, minimal changes by x-ray and an equivocal serum urate level. The first attack of gouty arthritis may appear in the first decade of life; usually the onset is a decade or two later. In exceptional instances, the first attack is delayed until the seventh or eighth decade of life. The earlier the initial attack develops the more severe the disturbance of uric acid and the greater the tendency to the development of chronic tophaceous changes. The disease is rather widely distributed, although the white race appears to be more susceptible. This may be related directly to the fact that there are better clinical statistics in those countries with predominantly white populations. The black race is relatively immune, although a number of well-documented instances of tophaceous gout have been recorded in Negroes. The yellow and brown races occupy an intermediary position regarding incidence.

ETIOLOGY

The etiology of gout has been the center of many polemics but an increasing number of observations support one mechanism among the several that have been proposed. It is generally accepted that the increased concentration of uric acid in the body, as reflected by the increased concentration

in the serum, is closely related to the underlying abnormality. The mechanism of the increased concentration is the point at issue. In the earlier part of the current century, *a differential inability of the kidneys to excrete urates* was proposed. It was a frequent clinical observation that minor or major renal dysfunction was present in patients with gout. The detection of albuminuria, a urate calculus, nitrogen retention or hypertension tended to focus on the kidney. It was reasonable to accept the hypothesis that there might be an impairment of excretion of uric acid by this organ to account for the retention by the body. As improved and more precise means for measuring renal function were developed, this explanation became less acceptable. The determination of glomerular filtration rate and tubular function revealed normal exchange of electrolytes, including urate, in most patients in the pretophaceous stage. Furthermore, some patients with tophaceous gout were shown to have normal renal activity. The determinations of urate clearance revealed that not more than 10% of the uric acid that appeared in glomerular filtrate found its way into bladder urine. The remainder, approximately 90%, was reabsorbed by the tubules. Only in the late stages of nitrogen retention did the gouty patient fail to maintain a normal urate clearance. Thus, a differential inability of the kidneys of gouty patients to excrete uric acid found meager support by students of the disease.

The second explanation, and an equally reasonable one, was an *impaired destruction* of uric acid by an enzyme system comprising uricase. Since the degradation product of uric acid in lower animals is allantoin, presumably the action of uricase in man would produce the same end product. Since only a few milligrams of allantoin are excreted daily by nongouty humans, a deficiency of the uricase enzyme system in gouty persons seems unlikely. Also, determination of the concentration of uricase in human tissues reveals relatively low values except for the liver and the intestines. The employment of N-15-labeled uric acid has detected some destruction in gouty subjects but no mechanism of impaired destruction accounts for the bulk of the metabolic dysfunction. With the lack of evidence in support of impaired excretion or subnormal destruction of uric acid, there remains yet a third explanation to account for the increased content of uric acid in the body. The *increased formation theory* is the favored one, not only because of the failure of evidence in

support of the first two mechanisms noted; more important is the positive evidence. An increased formation of uric acid by the body need be but slight to account for the observed chemical changes in the afflicted.

An increased excretion of uric acid in the urine has been observed from time to time in a number of patients with gout. From 300 to 500 mg. of uric acid may be recovered daily from the urine of a nongouty subject on a control diet that is relatively low in purine substances. Some patients with gout under similar conditions will excrete an additional 200 or 300 mg. A few gouty patients will excrete more than 1,000 mg. per 24 hours. Yet fewer will excrete as much as 2,000 mg. per 24 hours. Neither impaired excretion by the kidney nor deficient destruction by an enzyme system is believed to account for abnormalities of this magnitude. Recently, increased uric acid synthesis has been demonstrated by isotope studies utilizing N-15-labeled glycine (2). Ingestion of glycine labeled with this stable isotope results in a higher concentration of N-15 uric acid in the urine of victims of gout than in controls. The increased formation of urates develops at the expense of urea that proceeds through a more direct pathway or "shunt." It appears that a shunt will be demonstrated in some gout patients, but not all, whereby dietary glycine nitrogen enters the purine nucleus of uric acid more promptly than in the normal, presumably without the obligatory intervention of the nucleic acid purines. Although there have been no reliable clinical features in differentiation, Gutman and his associates (6) have speculated on the possibility of two types of uric acid disturbance in gouty patients. The metabolic defect, then, is a partial throwback to the normal situation in birds and reptiles, namely, a significant uricotelic component in a predominantly ureotelic species. The increased concentration of serum urate in nonaffected relatives is assumed to be caused by this trait. Patients with myelofibrosis or other blood dyscrasias, maladies known to be associated with an increased metabolism of purine substances, may develop gouty arthritis as a complicating malady. The articular and renal findings are similar to hereditary gouty arthritis.

Significant progress in our understanding of the *intermediary metabolism of uric acid* during the past decade may be recounted. Uric acid is the end product of metabolism of purine substances in humans, while urea is the end product

of the nitrogenous substances of amino acid and pyrimidine origin. Furthermore, it is generally accepted that mammals are capable of synthesizing purine bodies and converting them to uric acid. The constituents that may be incorporated in the purine ring, the basis of the "lactam" structural formula as postulated by Emil Fischer (5), include a number of simpler biologic substances. It has been shown that glycine furnishes carbon atoms 4 and 5 and nitrogen atoms 7, while carbon dioxide supplies carbon atom 6 and formate carbon atoms 2 and 8. Nitrogen atoms 3 and 9 come from the amide-nitrogen of glutamine, and nitrogen atom 1 comes from aspartic acid.

The initial reaction of glycine is a combination with phosphoriboxylamine to yield glycineamide ribotide. Several intermediates are then formed in the construction of inosinic acid. One of these compounds has been identified as 4-amino-5 imidozole carboxamide, which is converted to hypoxanthine. The synthesis does not produce free hypoxanthine, but hypoxanthine nucleotide or the compound identified above as inosinic acid. Hypoxanthine is synthesized initially; adenine and guanine are formed from it by amination. Guanine, at least, must be in combination with desoxyribophosphoric acid in synthesis since it has been shown that administered guanine is not incorporated into body nucleic acid. Hypoxanthine is oxidized by xanthine-oxidase to xanthine and, subsequently, to uric acid. The feeding of labeled glycine results in a higher maximal and a more rapid decline in the N-15 concentration in urinary uric acid in gouty subjects than in normals. The maximal values for N-15 uric acid are produced on the second day in gouty patients and on the third or fourth day in the controls.

Other studies utilizing N-15-labeled uric acid have yielded the functions, miscible pool (metabolic pool) and turnover rate, which have proved to be most critical in investigation of the disturbance of intermediary metabolism. The miscible pool of uric acid has been defined as that quantity of uric acid in the body which is capable of mixing promptly with intravenously injected uric acid and consequently of diluting its isotope. From a comparison of the concentration of N-15 in the uric acid injected and that present in the body at the moment of mixing, together with the knowledge of the quantity of uric acid injected, the quantity of uric acid present in the miscible pool may be calculated readily (12). It is pos-

sible to prepare uric acid labeled with N-15 in concentrations as high as 32% atom excess. Not more than 25 mg. of purified labeled uric acid is needed for a single isotope experiment. This amount may be injected intravenously as a neutral solution without untoward results. Complete urine samples are collected for approximately one week and are partitioned into four-hour or six-hour periods. The uric acid is isolated from the urine samples, converted to ammonia and the nitrogen isolated. Determinations of the ratio of N-15 (heavy nitrogen) to N-14 (naturally occurring nitrogen) is made in a mass spectrometer. It is presumed that all the uric acid in the body that participates in the metabolic pool is freely diffusible and that the rates of origin and disposal are equal. If the molecules of isotopic uric acid are indistinguishable from the naturally occurring molecules, the concentration of isotopes in the uric acid collected in the urine during the particular period is the same as the concentration of isotopes in the uric acid of the body pool during that period. Thus, the determination of miscible pool is not unlike the determination of blood volume following the injection of a known quantity of Evans blue dye. The metabolic pool, or miscible pool, of uric acid in humans has been found to be relatively constant in controls without a demonstrable disturbance of uric acid metabolism. In a normal person the pool size is approximately 1,000 mg.; the range, in the several laboratories in which this problem has been pursued, is from 730 to 1,340 mg. The turnover rate of pools per day, likewise, has been found to be relatively constant and has ranged from 0.5 to 1.0 pools per day.

These functions in patients with gout reflect the significant abnormalities predicted from the increased concentration of uric acid in the serum and the increased excretion of uric acid in the urine. The metabolic pool of urate in patients with gout, irrespective of the presence of acute or chronic symptoms, is greater by twofold or more than the controls. The turnover rate is somewhat less. In calculating metabolic pool, the deposits of uric acid in subcutaneous or osseous tophi have been largely ignored. Presumably there is some small interchange with the solid phase but this is not believed to affect significantly the measured functions. Since it may require a number of years for gross deposits to form, the exchange between urates in the precipitated phase with urates in solution is minimal. The observation that the dif-

fusible uric acid in body fluids in patients with gout is considerably above normal lends additional support to the belief that the basic metabolic fault is an increased formation of this substance in a gouty subject. The determinations of the metabolic pool and turnover rate have been used also in interpreting the mechanism of action of anti-gout agents, particularly those endowed with uricosuric properties. Benedict and associates (1) reported a marked diminution in the metabolic pool following prolonged administration of salicylates. ACTH and cortisone are mildly uricosuric agents and effect a modest change on the size of the metabolic pool. Bishop and associates (4) have investigated the persistent action of Benemid® on the metabolic pool. Their results indicate that so long as Benemid is ingested, a significant decrease in the metabolic pool occurs. Thus, no escape from this pharmacologic agent has been demonstrated throughout long-term administration.

The influence of diet on the disturbance of uric acid metabolism has received considerable attention, particularly because of the practical implications. The belief has been prevalent for many generations that a high protein as well as a high purine intake is harmful to gouty patients because of an increased excretion of uric acid in the urine that follows either of these dietary variations. It was presumed, without proof, that an increased excretion of uric acid in the urine most likely was accompanied by increased retention by the body and, as a result, harm ensued. There have been no studies showing that an increased protein or purine intake was associated with a significant increase in the metabolic pool which accompanied an increased excretion in the urine. It would seem to me to be just as logical to believe that supplementary nitrogenous foodstuffs would be endowed with a diuretic action for uric acid and benefit, rather than harm, would follow.

The concentration of uric acid in the serum of gouty patients is above normal—an observation slightly more than a century old. Whether the supplementary circulating urate is in the same physicochemical state as the normal fraction of this electrolyte has been the subject of considerable discussion. Some investigators have assumed that there are significant differences in the percentage of bound to total uric acid in gouty versus nongouty subjects. While there may be some differences, we believe that the clinical implications are not

affected and, that for all essential purposes, uric acid in the plasma circulates as the free ion. Urates are present in body fluids in concentrations somewhat less than the maximal solubility of sodium urate in distilled water. The limiting solubility in body fluids is due to the presence of other substances which contribute to the predisposition to precipitation in bones and soft tissues in afflicted persons.

The insolubility of uric acid has not always been a handicap to organisms. In fact, it has been of considerable teleologic value to birds and reptiles by permitting the successful development of the embryo in a hard shell. The waste products from nucleic acids and amino acids that were converted to uric acid could be excreted through the kidneys of the embryo as a dilute solution. The water was retained ultimately, leaving the uric acid as a solid mass. If highly soluble urea had been formed, instead of uric acid, the water could not have been absorbed against the gradient of the increasingly concentrated urea solution.

The determination of serum urate in the biochemical laboratory is associated with selected technical difficulties. Whole blood is a less desirable medium than serum or plasma for the determination, because of the unequal distribution of urates between cells and plasma, as well as because of the presence of interfering substances in red cells. The interfering substances complicate the development of color, the final step in the procedure. Because uricosuric agents frequently are prescribed for their anti-inflammatory properties during acute articular distress, equivocal laboratory results may follow. Salicylates are probably the most frequent offenders in this regard. Since salicylates are analgesic as well as uricosuric, and are present in a number of proprietary as well as ethical preparations used in the treatment of arthritis, prior ingestion may depress the concentration of uric acid to the borderline or normal range. In our clinic, blood for definitive values is not taken unless the suspected individual has abstained from any analgesic or uricosuric agent for a period of at least 48 hours. If this precaution is taken, and the determination is carried out by a skilled technician using fresh reagents, the results should be informative, not confusing.

The concentration of uric acid in serum in normals is less than 6 mg./100 ml. Irrespective of the presence of acute or chronic symptoms and irrespective of the stage of the disease,

the concentration in patients with gout should be greater than 6 mg. Of course, the only qualification is the prior administration of uricosuric agents. These include the more potent ones, such as salicylates and Benemid, as well as the less potent, such as phenylbutazone, ACTH and the adrenal steroids. Most of the patients with gout that we see in the clinic, before the administration of uricosuric agents, have a concentration of uric acid in the serum that ranges between 6 and 10 mg. The values may be as high as 14 or 16 mg. in unusual circumstances. In a rare instance the value is less than 6 mg. These statements apply particularly to males; the range in females is slightly less. Smyth and associates (11) suggest that the accepted range for females is approximately 0.5 mg. lower than for males. If this suggestion is followed, the upper range for normal females might be 4.5 mg. and the lower limit for gouty females would be 5.5 mg.

Although the concentration of serum urate may be above the normal range in a number of persons not suffering from clinical gout, these circumstances usually do not present themselves as problems in the differential diagnosis of gouty arthritis. Kidney insufficiency with retention of nitrogenous products, including uric acid, usually is not accompanied by acute joint distress. Note should be made, however, of the development of kidney disease in a limited number of patients with gouty arthritis. In such individuals, acute articular symptoms precede clinical evidence of renal disease and the diagnosis of gout should have been made a number of years earlier. Patients with myelofibrosis or other blood dyscrasias may show an increased concentration of uric acid in the serum as well as articular symptoms. This is believed to be secondary gout and not the coexistence of hereditary gout and a blood dyscrasia. Other conditions such as lobar pneumonia, pernicious anemia, coronary insufficiency and carcinoma, in which an increased serum urate level has been observed should not be diagnostic problems.

There are two conditions in which hyperuricemia may not be dismissed as readily. The incidence of idiopathic hyperuricemia is not known, but in our experience has been greater than had been presumed before the matter was investigated systematically. The sampling of adult males in a large general hospital has revealed a significant incidence of hyperuricemia. In the absence of a past history of gouty arthritis or a family history of this malady, the explanation is not

immediately available. Recently we have become interested in the incidence of hyperuricemia in patients with the garden variety of rheumatoid arthritis, particularly in males. It may be proved that some of these patients have idiopathic hyperuricemia quite unrelated to rheumatoid arthritis. Be this as it may, the finding of an elevated uric acid level in a patient with typical rheumatoid arthritis should not deflect the clinician from treating what most likely is the correct disease.

The mechanism of the *exchange of urates in the kidney* is well defined. The urate clearance of most gouty patients, irrespective of the stage of the disease, parallels closely that of nongouty controls, i.e., approximately 10 ml./min. Only a slight depression of urate clearance occurs in gouty patients despite a significant depression in glomerular filtration rate in those in whom this function has been observed. It is interesting to note that urate clearance tends to be maintained at the expense of per cent resorption as glomerular filtration rate is impaired by progressive renal damage. Berliner and associates (3) have investigated the possible role of a tubular resorptive capacity in regulating urate clearance and plasma urate concentration. An increase in urate clearance accompanied an increase in plasma level. It was revealed, however, that the magnitude of the urate resorptive capacity was so great that it probably could not be saturated in a normal individual. These studies are believed to be applicable to gouty persons without demonstrable renal impairment, which would be the state of all gouty patients in the earlier years of the natural history of the malady.

The mechanism of renal transport of uric acid has served as a useful investigative tool, particularly in reference to uricosuric agents. A number of these compounds have been tested, some for academic reasons only, others for their practical significance. The intravenous administration of Diodrast® is associated with a tremendous outpouring of uric acid. The resorption of urate by the tubules may be altered by as much as 50% with this agent. Obviously, this is not a practical solution to the correction of hyperuricemia in the gouty subject. The use of Benemid in maintenance doses (0.5–1.5 Gm. per day) results in an increased excretion of uric acid in the urine associated with a urate clearance that is approximately double the control value. This alteration of urate clearance precedes the decreased concentration of uric acid in the serum and persists so long as Benemid is admin-

istered. Phenylbutazone is a less potent uricosuric agent, but an analogue of this preparation (3.5-dioxo-1, 2-diphenyl-4-n-butyl-pyrazolidin sodium), when administered intravenously, results in urate clearances as high as 50 ml./min. There is no alteration in glomerular filtration rate during uricosuria. The potential toxicity may be the limiting factor in the long-term administration of this agent. The paradoxic retention of uric acid by uricosuric drugs at low dosage has been restudied by Yü and Gutman (16). Salicylates, phenylbutazone and Benemid were perfused intravenously at low plasma levels. Rather than an increase in urate clearance, a depression of this function resulted. Colchicine has no demonstrable effect on urate clearance in gouty or nongouty subjects.

PATHOGENESIS

The pathogenesis of acute articular gout continues to be an enigma. Most likely, urate infiltration of joint structures precedes the acute articular attacks. We have observed large deposits of uric acid in articular and periarticular spaces in patients with a meager clinical history of acute symptoms in the joints under study. This leads us to believe that the deposition of sodium urate in the gouty subject is rather extensive and that the acute articular episodes are not associated with the presence *per se* of uric acid deposits (Plate 2, p. 17). There are a number of patients in our clinical series who have adhered to the prophylactic regimen for several years without experiencing any acute articular distress. These patients have subcutaneous tophi as well as osseous tophi as demonstrated roentgenographically. Nevertheless, so long as the prophylactic regimen is maintained, they remain symptom-free. Increased precipitation of uric acid crystals may occur during an acute attack but this supposition lacks proof. The mere presence of uric acid crystals during an acute attack is not convincing evidence to us that they are the cause of the articular distress. Except for secondary changes usually attributed to inflammation, I believe that the physical appearance of the articular tissue at the time of the acute attack resembles that in the intercritical period.

CLINICAL FEATURES

The clinical features of the acute attack of gouty arthritis are characteristic and should be identified readily in most

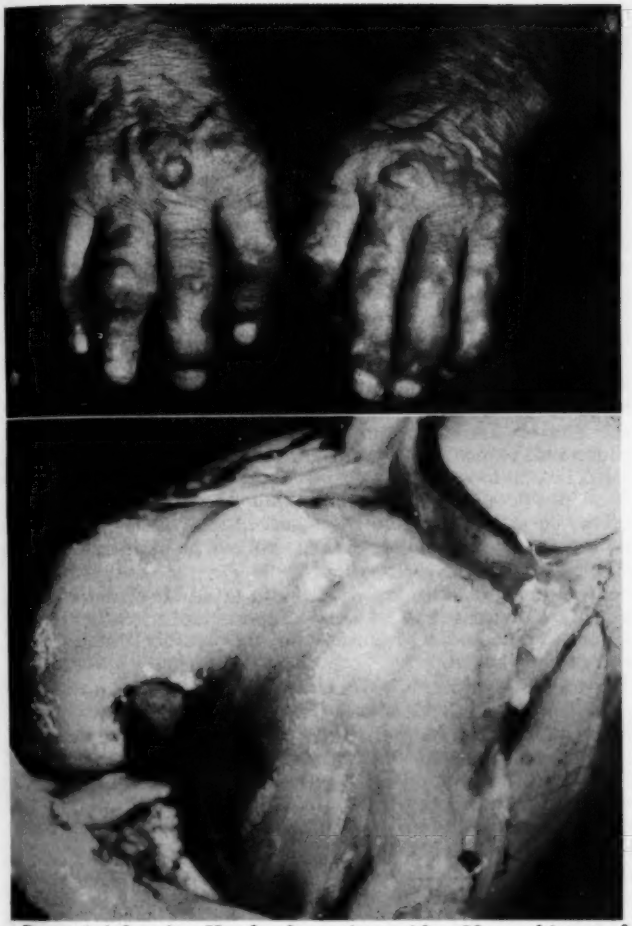

PLATE 1 (*above*).—Hands of a patient with a 30-year history of gouty arthritis.

PLATE 2 (*below*).—Postmortem specimen of knee, showing extensive urate deposits.

instances. The diagnosis probably will not have been suspected until after the initial articular episode nor should a diagnosis of gout be made until after this morbid event. There are selected symptoms or findings, however, that may precede articular distress and might point the way for the critical clinician. Albuminuria, elevation of blood pressure and the passage of a renal stone, respectively, have been observed before the first articular bout. Since the disturbance of uric acid metabolism is a persistent phenomenon, and these items may be observed following the articular episode, it is not surprising that sometimes they may precede the first attack of acute gouty arthritis. The typical episode of acute gout embodies the sudden onset of severe pain in one of the peripheral joints of a male. This may appear at any time of the 24 hours of the day in any day of the year. The onset of symptoms is sudden, the pain is excruciating and the patient is extremely miserable as a result. One or more joints may be involved simultaneously or several joints may be involved successively and simulate the migratory polyarthritis of acute rheumatic fever. The presence of cardinal signs of inflammation, i.e., redness, swelling, heat and tenderness, suggest an acute septic process. The metatarsal-phalangeal joint of the great toe remains as the most susceptible structure. Ankles, wrists, elbows and knees usually follow in incidence in this order. Rarely is the hip or shoulder or spine affected. Although acute attacks usually are confined to articular structures and associated with edema, a subcutaneous tophus, a bursa or a tendon infiltrated with urate may be acutely involved and extremely painful.

Systemic symptoms associated with an acute attack comprise fever, chills, malaise, headache and tachycardia. A leukocytosis and an increase in the sedimentation rate may further confuse the differential diagnosis between acute gouty arthritis and a septic process. If the knee is involved, a large effusion may accompany the acute symptoms. The duration of an attack is unpredictable if specific measures are not instituted early. The first attack may be of short duration and subside within a few hours, as rapidly as it appeared, or it may persist for several days or even several weeks. Proper management of the acute attack should result in prompt improvement, partial rehabilitation within 24 hours and essentially normal function within 72 hours. On the other hand, if the attack is severe and inadequately or

poorly treated, one or more weeks may elapse before partial function is restored. Desquamation of the surrounding area may follow an acute attack. The joints involved in the acute attack usually are confined to the hands or feet.

PRECIPITATING FACTORS

Premonitory symptoms were stressed in the older literature; precipitating factors are, in our opinion, more significant. Vasomotor instability, flatulence, epigastric distress, depression, insomnia and palpitations, if present, should be heeded but are unreliable precursors. Although gout has been attributed to overindulgence in food and alcohol, the hereditary nature of this malady is believed to be more vital. The presumption that particular foods, except for those of high purine content, are harmful to gouty patients is a prejudice. Even foods high in nitrogenous and purine substances are not reliable as provocative agents. More reliable factors include an acute infection, direct trauma, blood loss, myocardial infarction, exposure to the elements, a surgical operation, emotional trauma and drugs. Parenteral penicillin should be prescribed to gouty patients only if there are sound clinical indications for its use, since administration of this antibiotic may be followed by an acute gouty attack. Thiamin chloride, vitamin B_{12}, insulin, ergotamine tartrate and mercurial diuretics are in the same category.

The interval between attacks is largely a function of adherence to the prophylactic regimen as described later. In former years, there was a relatively good correlation between severity of the metabolic disturbance and the incidence of acute attacks. With the utilization of colchicine, the availability of Benemid and the knowledge of the prophylactic value of the combination, the intercritical period will be prolonged markedly. However, some patients mildly afflicted may suffer little or no distress year by year without periodic ingestion of colchicine or without adherence to the colchicine-Benemid regimen. These represent the exception rather than the rule.

Chronic tophaceous gout is observed in but a small percentage of patients in our experience. The presence of subcutaneous tophi does not mean persistent symptoms of chronic joint involvement. Sometimes tophaceous deposits interfere with motion of joints and low-grade distress per-

sists. We have had only two patients, in our experience of more than 20 years, who have become bedridden because of gouty arthritis. In each case incapacity appeared several years before Benemid was available. Large subcutaneous tophi may develop about the elbows, knees, hands or feet but usually are unattractive cosmetically rather than important medically (13). Eventually the recognition of chronic tophaceous gout should be of historical interest only.

COMPLICATIONS

The complications of gout are centered about the kidney (Plate 3, p. 21). Despite the frequency of kidney impairment, this becomes a major clinical problem infrequently. The detection of kidney trouble in a routine urine examination, or the histologic evidence of structural changes postmortem, does not imply critical dysfunction in the respective examples. Almost 50% of the patients with gout seen in this clinic have some evidence of renal dysfunction. Mild albuminuria, cells or casts in the sediment and a modest elevation of blood pressure comprise the bulk of the findings. The number of patients who have died prematurely because of renal impairment associated with gout is small in our clinical experience. Evidence of kidney involvement in the late stages of renal insufficiency includes impairment of concentrating ability, increased concentration of blood urea nitrogen, impaired excretion of phenolsulfonphthalein dye and function determined by intravenous pyelography. When persistent nitrogen retention is observed, it is a late manifestation. The interval between the appearance of albuminuria, usually the first evidence of renal dysfunction, and the development of nitrogen retention may be several decades. Such a protracted course of nitrogen retention is characteristic of gout. There are a few patients whom we are following who have nitrogen retention year after year without any significant progression —an observation that would be highly unusual if the nitrogen retention were associated with chronic glomerulonephritis. Approximately 5% only show a persistent increase in the concentration of blood urea nitrogen.

Various terms applied to the kidney involvement in gout indicate a lack of definitive characteristics, clinical as well as pathologic. The mechanism of the renal disturbance is believed to be initiated by the precipitation of sodium urate

PLATE 3.—Postmortem specimen of kidney, showing urate deposits.

from a supersaturated glomerular filtrate. Blockage of the tubular lumen, degeneration of the epithelium, atrophy of the nephron and destruction of the glomerulus follow. The small vessels in the parenchyma share ultimately in the degenerative process. Regression in glomerular filtration rate and depression of renal blood flow follow eventually. A kidney repeatedly subjected to insult from the precipitated crystalloids is more susceptible to pyogenic organisms. Thus, pyelonephritis sometimes develops and if urea-splitting bacteria are the invaders calcium stones may result.

Although calcium stones theoretically might develop in patients with gout under these circumstances, most stones have a high urate content. Approximately one in seven patients with gout suffers from renal colic or passes a renal stone. One of the most famous sufferers from gout, Benjamin Franklin, was severely troubled with urate gravel and a bladder stone. The effect of contemporary treatment on the incidence of urate stones is an important clinical problem. Uricosuric agents which lead to an increased excretion of uric acid in the urine are potential stone formers. Since precipitation of uric acid in tubular urine is a function of solubility in available fluid, increased fluid turnover nullifies the tendency to stone formation. It is our clinical impression that the incidence of uric acid stones is no greater during the past few years than it was before Benemid became available. Phillips (9) believes that Benemid may reverse some of the histologic changes produced by the increased uric acid turnover in gout. We have no evidence to support this observation but concede that the possibility of partial restoration is reasonable.

Hypertension and arteriosclerosis are considered by some observers to be integral aspects of gout. Hypertension is a relatively common finding but follows the pattern of a benign, rather than of a malignant type. One explanation for the hypertension is the relation to renal damage. The association of arteriosclerosis, and especially coronary sclerosis, in gout is more equivocal. I do not believe that patients with gout are more prone to the development of coronary artery disease than nongouty individuals. With gout we are dealing with middle-aged males, and this group appears to be susceptible naturally to coronary disease. To attribute atherosclerosis or sclerosis of the coronary vessels to an increased amount of circulating uric acid is believed to be highly speculative. On

PLATE 4.—Foot of a patient, showing scattered osseous tophi.

PLATE 5.—Foot of a patient with chronic tophaceous gout.

the other hand, large vessel sclerosis develops prematurely in some gouty patients. Since x-rays of the feet usually are taken in patients with gout, we have had the opportunity to observe a number of patients with large vessel calcification which appears to be unrelated to vascular deficiency in the extremities. Until recently, we had not seen a patient encounter trouble from an arteriosclerotic aneurysm of the abdominal aorta. During the past year, however, we have known of two deaths in gouty patients with this complication.

DIAGNOSIS

The diagnosis of chronic tophaceous gout in a patient who has suffered several acute attacks should be self-evident. The diagnosis at the time of the first attack usually is the clinical problem. In considering the possibility of gout to explain an acute articular episode, a positive family history, the history of a urate calculus, the presence of albuminuria or hypertension are ancillary features. Preliminary information concerning each of these items should not be difficult to obtain and if one or more is positive suspicion of acute gout is justified and warrants the pursuit of the several critical criteria. The clinical features of the acute attack are probably the most helpful of any in diagnosis. The sudden onset of severe pain in one or more peripheral joints of the extremities in a previously healthy male probably means gout until disproved. The concentration of uric acid in the serum is helpful but is not exclusively diagnostic. The increased concentration precedes the acute attack, is observed during the acute attack and is present in the intercritical period, save for the administration of uricosuric agents. This diagnostic procedure is particularly helpful in patients who have not developed subcutaneous or osseous tophi.

The response to colchicine is another helpful criterion. Colchicine is specific for acute gouty arthritis and has little or no effect on other forms of joint disease. In a suspected case of gout a full course of colchicine should be administered, as noted under Treatment. Most patients with acute gouty arthritis respond and the diagnosis seems evident. Since salicylates, steroids and phenylbutazone are nonspecific antirheumatic agents they are less helpful, therefore, as a combined diagnostic and therapeutic guide. If colchicine is prescribed for diagnostic information, full therapeutic amounts must be

given, i.e., up to the point of gastrointestinal distress. Inadequate quantities of colchicine may provide little symptomatic relief and may give a misleading diagnostic answer.

The search for cystic areas in the peripheral joints of the extremities should be made in any suspected case of gout but will be negative in the early or mild case. The metatarsal-phalangeal joint of the great toe is one of the first structures to show chronic changes by x-ray (Plate 4, p. 23). One or more small lesions may appear in the head of the metatarsal of the great toe. As the disease progresses, a number of tophi may be observed. Diminution of joint space and ankylosis are late manifestations and are observed infrequently (Plate 5, p. 24). Calcium salts are replaced by sodium urate and increased radiability of the involved area results. Tophi must attain a considerable size, perhaps 5 mm. or greater in diameter, before they are visible by x-ray and their identity reasonably assured. During the past few years we have employed a magnification technic which has increased our interest in roentgenography in bone and joint disease but has not altered our diagnostic criteria in gouty arthritis. Since x-ray changes are not present in the earlier years of articular distress, several attacks of acute arthritis usually precede the development of roentgenographic changes. A number of patients with a long history of intermittent attacks may present normal roentgenographic findings in the affected parts.

Subcutaneous tophi, usually in the ears, appear many years after the initial attack. Patients with a severe form of the malady may have subcutaneous tophi adjacent to and involving most of the joints of the hands, feet, elbows and knees. The skin overlying a periarticular tophus may be bruised and urate sludge allowed to escape. The metatarsal-phalangeal joint of the great toe and the terminal phalanges of the fingers are especially susceptible to this complication.

PROGNOSIS

The prognosis in gout is the most satisfactory of any of the severe forms of joint disease. Prior to recent years, it was generally believed that the more frequent the acute attacks the more rapid the progression of the disease and the greater the probability of the development of chronic deforming changes. This view was particularly applicable to the gouty patient in whom the onset of articular distress occurred in

adolescence or early adulthood. Patients who experienced the onset of articular symptoms in the declining decades of life usually fared much better. It was also believed that the larger the metabolic pool the greater the tendency for an early onset of articular symptoms and the more extensive the deposition of sodium urate in and about the joints. While, at the present time, factors contributing to the size of the metabolic pool are not susceptible to alteration, clinical effects of the increased metabolic pool may be modified significantly. Patients who adhere to the prophylactic regimen suffer less and less articular distress year by year and, in most instances, are able to live quite normal lives. The only exception is the patient with renal disease. Uremia is a determining factor in a few patients. Critical renal impairment, unrelated to the severity of chronic tophaceous arthritis, may lead to premature death. In addition to the direct effect of urate deposition in the kidney, complications such as pyelonephritis, vascular changes and amyloid deposits contribute. However, if renal disease or hypertension appears in a patient with gout, it is believed that the prognosis is somewhat better than if either of these findings was attributed to chronic glomerulonephritis.

TREATMENT

The treatment of the articular dyscrasia will be considered in (1) the acute phase and (2) the intercritical phase. If a correct diagnosis has been made, current treatment will be rewarding. Although gout is a chronic disease with a tendency for articular symptoms to remain in each susceptible individual, irrespective of the efficacy of therapeutic agents, richer dividends may be anticipated in the treatment of gouty arthritis than in any other major type of joint disease. Management of the intercritical period will be considered first because it is believed that prevention of acute attacks should take precedence over treatment of them. Although the acute episode is an unhappy event for the afflicted, proper respect for the prophylactic regimen in the intercritical period will reduce the incidence of acute attacks to clinical insignificance. Thus, the intercritical period should occupy the greater portion of the time of the afflicted individual. If the prophylactic regimen is followed, the patient should live a normal life and progression of the basic metabolic disturbance should be clinically unimportant.

This phase of the management of gouty arthritis is concerned with the regular administration of two of the most effective anti-gout agents, i.e., colchicine and Benemid. Although each is essential to the regimen, it is the combination that has been responsible for the excellent clinical results in recent years. Each drug complements the other; neither one by itself is so effective. The other anti-gout agents may be disregarded in prophylaxis if colchicine and Benemid are taken regularly. The systematic use of colchicine as a prophylactic agent has been advised for a number of years in our clinic; the discovery of the uricosuric action of Benemid and its clinical application are more recent observations. It should be appreciated that it is the combination of colchicine and Benemid, each resulting in specific effects, that is responsible for the successful result in the intercritical phase (Fig. 2).

The mildly afflicted may take not more than a few milligrams of colchicine per month. The moderately afflicted should ingest 0.5 or 1 mg. of colchicine daily. The severely afflicted should take colchicine up to tolerance. Several patients in our series have ingested from 1 to 1.5 mg. daily for a number of years; there are a small number who have taken as much as 2 mg. of colchicine daily for more than a decade. The daily use of this preparation in the intercritical period has proved to be extremely beneficial although little or no effect on uric acid metabolism may be attributed to colchicine. In prescribing such amounts of colchicine daily, it is important to inquire whether or not intolerance develops or delayed toxic symptoms appear. In each instance, the answer is in the negative. Colchicine is endowed with negligible toxicity and is one of the most respected drugs in the pharmacopeia when used in therapeutic amounts as described. Intolerance to the drug does not develop and when an acute attack appears a full course of colchicine is maximally effective, irrespective of previous ingestion. The only exception is the circumstance in which the susceptible person is on the borderline of gastrointestinal irritability from the daily ingestion of colchicine. A full course may not be tolerated in such an individual because of the premature appearance of nausea, vomiting or diarrhea. Patients who have been on daily rations of colchicine for a decade or more receive the optimal benefit from a full course when this is prescribed. Hence, it is important that the quantity of colchicine ingested daily be maintained at a level that will not compromise the intestinal tract.

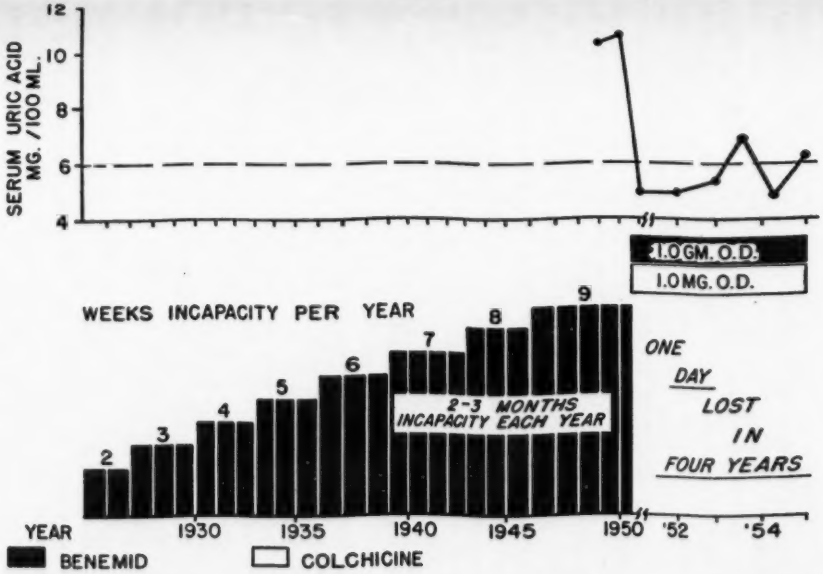

FIG. 2.—Days of incapacity before and during the prophylactic regimen (moderately severe gout).

Another obvious gain in the ingestion of colchicine regularly is the advantage in having started a course at the earliest possible moment should acute symptoms develop. Patients should never find themselves without a supply of colchicine tablets. Until such a time as a more effective anti-inflammatory drug is devised, colchicine will maintain its pre-eminent position as a prophylactic anti-gout agent.

Colchicine stood alone as the prophylactic drug of choice until recently and, except for salicylates and cinchophen, lacked a companion preparation which possessed a persistent and powerful uricosuric action. Salicylates and cinchophen did not fill this void. Hence, when probenecid (Benemid) was devised, following the observation of Wolfson and associates (15) that caronamide possessed uricosuric properties, an important step was taken. Selected patients with a long history of intermittent attacks of severe gouty arthritis, as well as others with a milder form of the disease, were prescribed Benemid initially in 1950 and have taken this preparation daily for almost seven years. More patients were placed on it as our confidence in the drug increased and, eventually, Benemid was prescribed to all patients suffering from moderate or severe gout. Since many of our patients had been on colchicine regularly, satisfactory control data had already been accumulated. The addition of this new drug to the prophylactic regimen introduced a variable, the results of which could be determined readily. It should be stressed that colchicine continues as one of the two foundation stones in the prophylactic regimen and the administration of Benemid in no way obviates the need for colchicine. We possess no clinical data on the use of Benemid without colchicine. A few instances have been reported to us of this situation with disappointing results. Thus, Benemid by itself is only partially effective. It is the combination of Benemid and colchicine that is maximally so.

The dose of Benemid recommended for daily consumption has been decreased somewhat as we have gained additional experience with this agent. We proceeded originally on the assumption that the larger the quantity of Benemid ingested, the greater the uricosuric action and the greater the inhibition of the tendency to urate precipitation in bony and soft tissues. This assumption still appears to be sound theoretically, but clinical experience has been almost as satisfactory with less than maximally tolerated doses. Currently we pre-

scribe from 1.5 to 2 Gm. of Benemid for the person severely afflicted with chronic tophaceous gout and approximately 1 Gm. a day for the moderately afflicted individual. Throughout the high dose regimen, the value of an abundant fluid intake, in order to inhibit precipitation of urates in renal tubules, has been stressed. If more uric acid is excreted per day, the solubility may remain unaltered if the fluid output is increased proportionately. The clinical benefit that accompanies the administration of Benemid becomes increasingly more encouraging year by year. There are two actions that may be attributed directly to Benemid and two actions to the combination of colchicine and Benemid. An increased excretion of uric acid in the urine and a decreased concentration of uric acid in the serum are the anticipated pharmacologic effects of Benemid. A maximal change occurs shortly after beginning medication and equilibrium tends to be established and maintained, year by year, so long as Benemid is ingested daily. At the higher dose levels of Benemid, a significant decrease in the concentration of uric acid in the serum and a proportionate increase of uric acid in the urine is observed. A number of patients who are taking Benemid daily have a uric acid that persists in the normal range while previously it was several milligrams higher. The second direct effect of Benemid is the decrease in the size of subcutaneous tophi and recalcification of the punched-out areas in the bone, areas of urate deposition that have slowly replaced calcium salts. We do not rely on Benemid to reduce large subcutaneous tophi, since we prefer surgical excision—a more rapid process. Regression of osseous tophi, as determined roentgenographically, continues slowly but surely.

The most important subjective evidence of the benefit of the combination of Benemid and colchicine is the diminution or elimination of acute attacks of gout. Although acute attacks have appeared at times in patients, irrespective of the adherence to the prophylactic regimen, the reduction in incidence of acute attacks is statistically significant. It is mildly discouraging to the patient to observe an acute attack during the first few weeks after beginning Benemid. Originally it was our impression that there was a slightly increased incidence during this period. Now we question the variability and believe that the attacks would have occurred in any case. The appearance of acute attacks while on a uricosuric agent with a normal level of uric acid in the serum is an interesting

observation that confirms the impression, stated some years ago, that the absolute level of uric acid in the serum is not the determining factor in the etiology of the acute attack of gout. From four to six months after beginning the prophylactic regimen there is an unchanged or slightly decreased frequency of attacks. Thereafter, the marked diminution in incidence is gratifying. A number of patients who have taken colchicine and Benemid for a period of almost seven years, with a past history of moderate or severe gouty arthritis, have not lost a day from work because of acute articular gout during this time. The majority of patients, irrespective of the severity of the disease, average less than one day of incapacity per year. This represents a striking reduction in the incidence of attacks. Another effect of the combined medication is an improved feeling of well-being, not noted while colchicine was the only drug administered regularly. It is believed that this well-being represents a dividend in addition to the decreased incidence of acute attacks. Also, it contributes to the reassurance that has replaced the perpetual fear of an acute attack developing on a moment's notice and without warning. Whether this improved state of well-being is related directly to the decrease in the metabolic pool remains to be determined. There may be other factors, not yet defined, that are responsible.

The incidence of toxicity and the number of patients who are forced to discontinue Benemid are unimportant clinically. Gastrointestinal distress may be prevented by the ingestion of Benemid with meals. Two patients in our series developed a skin rash; one of them, refusing to hold the drug responsible, continued to use the drug. The second patient developed pruritus which subsided after cessation of the drug and did not reappear after reinstitution of the medication. One severe case of anaphylaxis has been reported in the literature, but this also was no contraindication to desensitization subsequently. The administration of Benemid to patients with demonstrable renal impairment is a pertinent and practical problem. Since a significant percentage of patients show evidence of renal dysfunction, these patients might be deprived of great benefit if Benemid were found to be harmful. Our observations have been reassuring and we have prescribed Benemid when indicated, irrespective of the detection of nitrogen retention.

The length of time that a patient should be on Benemid

daily has not been determined. It is our prediction that patients severely afflicted will be advised to take Benemid indefinitely. Patients moderately afflicted probably may revert to smaller doses with safety, meanwhile ingesting some colchicine as anti-articular prophylaxis. Patients mildly afflicted have been taken off Benemid for varying periods, after adherence to the regimen for two or more years. These patients, however, have continued to take small doses of colchicine regularly, as noted above. Since the combination of colchicine and Benemid cannot be considered a cure, it is believed that most patients with gout should take modest quantities of each of these compounds regularly.

General measures during the intercritical period include attention principally to fluids and foodstuffs. A high fluid intake is imperative. Tap water should suffice in most instances. Fluids with caloric supplements, such as milk or ginger ale, are adequate, but since gouty patients tend to gain weight the additional caloric intake may be undesirable. Patients with gout should develop the habit of drinking liberal quantities of tap water or alkaline water at mealtime as well as between meals. The quantity consumed in the evening should be regulated to avoid nocturia. Probably a minimal urine output, if the patient is taking Benemid, should approximate 2 liters per day. This amount of urine necessitates an ingestion of fluids considerably greater. Coffee, tea or cocoa need not be restricted. Also, there is meager evidence only that alcoholic beverages consumed in moderation aggravate the metabolic disturbance. An occasional patient may produce satisfactory proof that a particular beverage acts as an inciting agent for an acute attack. Obviously such an offender should be avoided. Most patients, on the other hand, irrespective of the severity of their gout, are able to remain in a symptom-free state, meanwhile enjoying a temperate intake of alcohol if they so desire and if the critical anti-gout measures are respected. We believe that the harm from alcohol comes from the quantity consumed, rather than the quality. The current generation of gouty patients, in keeping with long-established traditions, appear to enjoy alcohol before or during meals. The majority of patients appreciate the liberties provided and the incidence of attacks is not increased.

A liberal policy in regard to eating is followed also. In reference to the older writings on the management of gouty arthritis, it has been recorded that each kind of foodstuff has

been condemned and prohibited by some physicians as well as praised and recommended by others. It is of some interest that the current edition of one of the best textbooks of medicine contains a full-page listing of the purine content of certain foods and specific recommendations as to the quantity that may be consumed weekly or daily. An equally popular textbook devotes five lines to the same subject. It is little wonder that some physicians tend to be confused by dietary admonitions in this disease. We believe that the benefits from a low-protein and a scrupulously low-purine diet have been overemphasized. There are several instances of patients in our series who have religiously, and for a number of months, consumed a low-protein and low-purine diet, but have not taken colchicine and have suffered prolonged periods of incapacity during this regimen of abstinence. With a modification of their regimen, by the addition of colchicine, Benemid and proteins, the clinical situation has been altered strikingly. Not only are our clinical observations favorable to a liberal intake of varied dietary foodstuffs, but investigations using isotope technics have helped remove some of the stigmata from proteins. Recent observations in the laboratory suggest that proteins may be no worse offenders as precursors of uric acid than are carbohydrates and fats. Some of the simpler biologic substances such as carbon dioxide, formic acid, glycine, lactate and ammonia may contribute a nitrogen or a carbon atom to the uric acid molecule in the intermediary metabolism of this substance in the body. The therapeutic implications regarding dietary restrictions in gouty patients are affected profoundly by these experimental data. It is apparent that carbohydrates, as well as proteins and fats in the diet, are potential precursors if carbon dioxide and formic acid contribute to the uric acid molecule in the human economy. It is reasonable to assume, however, that some precursors may contribute to the uric acid molecule to a greater extent than others. It is appreciated that proteins and some nucleoproteins which yield pyrimidine bases form urea as the nitrogenous end product, not uric acid. Only those foods high in purine substances such as liver, kidney, sweetbreads and anchovies are restricted. A diet balanced in content of fats, proteins and carbohydrates has been recommended for more than two decades (14) and empirically is desirable, not harmful. The caloric content is believed to be as important as the specific items. A few gouty patients tend to be overweight;

this imposes a burden on the cardiovascular system as well as the weight-bearing joints. General rules for the maintenance of a normal body weight are believed to apply in gouty arthritis as well as in a number of other maladies.

Treatment of the acute attack has been placed in a position of secondary importance in recent years. If proper deference has been paid to the prophylactic preparations, the acute episodes should be infrequent in incidence and mild in severity. The most valuable drug in the treatment of the acute attack continues to be colchicine. It is used either exclusively as a "full course" or is combined with phenylbutazone or ACTH. The use of colchicine alone will be discussed initially since the anti-gout agent selected in the unconfirmed case may carry diagnostic implications as well as therapeutic value. The quantity of colchicine prescribed should be based on the severity of articular symptoms. The subsidence of distress in a mild attack may follow ingestion of not more than four or five single doses of the 0.5 mg. strength. A moderate or severe attack requires the "full course." This is achieved only by the periodic ingestion of colchicine until the onset of gastrointestinal distress. Either one tablet, 0.5 mg. strength, may be ingested every hour, or two tablets, 1.0 mg., every two hours, without interruption until the anticipated side effects appear. It is important for the patient to consider the severity of the attack at the onset of symptoms. A mild attack may be suppressed with a few colchicine tablets if the treatment is started early. A severe attack may be adequately and properly managed with colchicine only through a full course. A mild attack may be handled without interruption of daily routine and probably without medical advice if the patient has been properly coached. Each patient should be instructed to proceed with a full course of colchicine once the possibility of a recurrence of acute symptoms is entertained. The usual number of colchicine tablets that comprises a full course varies between 10 and 14, taken over a span of the same number of hours.

There is no satisfactory explanation for the obligatory induction of gastrointestinal symptoms in order to achieve the full therapeutic effect. The clinical observation, however, is well substantiated. There is general agreement that the full therapeutic action of colchicine is accomplished in the severe attack only if unmistakable gastrointestinal distress has been provoked. Patients who attempt to circumvent this distress

by the ingestion of smaller quantities of colchicine or who take colchicine over longer periods receive submaximal benefit. The involved joints usually begin to improve near the close of the full course and become progressively less painful hour by hour. If it is necessary to repeat the course, and it is in a limited number of instances, a lapse of 48 hours should take place. If oral colchicine is ingested prior to this lapse of time, an adequate amount of colchicine will not be tolerated and frustration ensues. The failure to appreciate the proper method for administering colchicine has been partially responsible for its unenthusiastic recommendation by some physicians and restricted use by their patients. The necessity of producing gastrointestinal distress has contributed to its unpopularity which, although unpleasant, does not constitute a contraindication. At the onset of this side action, ingestion of colchicine is to be stopped, irrespective of the subsidence of joint symptoms, and a gastric sedative ordered. Tincture of camphorated opium, 5 ml., is recommended by us and the dose repeated every two or three hours as needed.

Although colchicine is believed by us to be the essential drug in the treatment of the acute episode, other agents have been recommended and combinations of colchicine with other drugs have been used. Phenylbutazone is an effective anti-inflammatory and analgesic drug and although not specific for gout is valuable nevertheless. Some physicians recommend it as the only drug in the treatment of the acute attack; when we use it, it is in conjunction with colchicine. If a patient has been on the colchicine-Benemid prophylactic regimen for a relatively short period, the full effects of these agents will not have become manifest and acute attacks will continue to be a serious problem. In such a circumstance, less than a full course of colchicine is prescribed (2–3 mg.), together with 800 mg. of phenylbutazone during the initial 12 hours. A similar quantity of phenylbutazone is given 24 and 48 hours later. If an adequately or poorly treated attack of gout has responded less than maximally to a full course of colchicine, supplementary phenylbutazone may be helpful. Lastly, low-grade symptoms sometimes may persist following a colchicine-treated attack if treatment has been delayed for several days. In addition, phenylbutazone may be recommended for a period of two or three days. The toxic effects of phenylbutazone when used for short periods are not serious. Even the stanchest advocates advise caution in the long-

term use of phenylbutazone. Adrenocorticotropin and the adrenal steroids are of restricted value in the treatment of acute gout. The newest adrenal steroids, prednisone and prednisolone, have been less effective in our experience than ACTH. We have never advised ACTH as the sole drug in the treatment of the acute episode, using it only in conjunction with colchicine. From 60 to 100 units of the ACTH-gel may be given for two or three days as an adjuvant.

General measures for the treatment of the acute attack include a light diet, an abundance of fluids and rest of the affected joints. Since a severe attack may be associated with a significant increase in body temperature and an increased loss of sensible perspiration, an augmented fluid intake serves a dual purpose. Replacement of fluid lost by way of the sweat glands is imperative. Equally important is the need for an adequate quantity of fluids for renal transport of uric acid in order to minimize the tendency for the precipitation of urates in the tubules. This usually may be accomplished by tap water. No useful purpose is served if severely affected joints are kept active or subjected to weight-bearing so long as acute symptoms persist. Restriction to a chair or bed is imperative if one or more joints of the lower extremities are severely involved. A cradle for the bed covers is desirable. Local application of moist dressings, dry heat or cold compresses serve no useful purpose.

The *surgical treatment* of chronic tophaceous gout is applicable to a few patients. Large subcutaneous tophi which have become unsightly, as well as smaller tophi of the hands and feet which interfere with the wearing of gloves and shoes, may be removed. Tophi in exposed areas of the body, such as about the olecranon process, the patella and the heels, are unsightly as well as potential sites for sinus formation. Tendon involvement by tophi which interfere with motion or locomotion also indicates surgery. In removing tophi from the subcutaneous tissues it is important to carry out extensive curettage of the urate deposits. The failure in the past by some surgeons to obtain a good postoperative result is believed to be related partially to the failure to remove adequately the urates in the operative field. The surgical treatment of a discharging urate sinus involves little or no risk from postoperative infection. Even before the antibiotic era the incidence of postoperative infection was negligible. It should not be forgotten that parenteral penicillin probably is

contraindicated because of the possible induction of an acute attack of arthritis. Most helpful in the medical management of a gouty patient undergoing surgery is the preoperative administration of 1.5 mg. of colchicine daily, for three or four days, if the patient is not already on rations of this magnitude. A similar quantity should be given for three or four days following surgery.

SUMMARY

During the past 20 years considerable progress has been made in the clinical study, laboratory investigation and treatment of patients with gouty arthritis. This malady is one of the commoner types of arthritis and may be recognized at the time of the first attack of articular distress. If it is recognized and proper treatment recommended, acute symptoms should subside and restoration of function be complete. The prophylactic regimen of colchicine and Benemid has been highly successful in our experience and thereby is responsible for successful management of a potentially crippling disease.

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